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| 10/608,863 | 06/27/2003 | Ryoichi Hashida | 3462.1003-000 | 8202 |

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| EXAMINER | |
|---|---|
| HOWARD, ZACHARY C | |
| **ART UNIT** | **PAPER NUMBER** |
| 1646 | |

DATE MAILED: 11/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/608,863 | HASHIDA ET AL. | |
| | Examiner | Art Unit | |
| | Zachary C. Howard | 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,4-30 and 32-57* is/are pending in the application.

4a) Of the above claim(s) *4-30 and 32-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 54-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,2, 4-30, 32-57* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 June 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Application, Amendments and/or Claims*

The amendment of 9/16/05 has been entered in full. Claim 1 is amended. Claims 3 and 31 are canceled. New claims 54-57 are added.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This application contains claims 4-30 and 32-53 drawn to an invention nonelected without traverse in Applicant's response filed 2/14/05. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1, 2 and 54-57 are under consideration in the instant application.

### *Specification*

The new title is accepted.

### *Information Disclosure Statement*

Applicants' arguments at pg 14 of the 2/14/05 response regarding references AM, AO and AQ from the IDS of 6/72004 are noted. The request for Applicants to submit each reference is withdrawn in view of Applicants' persuasive arguments, and the Examiner has considered each reference. However, because the Examiner has crossed these references off of the IDS of 6/7/2004, and which is now part of the record of the application, Applicant is requested to submit a new IDS listing each of these three references for the Examiner to initial and have scanned into the record, so that any patent issuing from this application will indicate that said references were submitted by Applicant. A copy of each is reference is not required to be submitted with the new IDS.

***Withdrawn Objections and/or Rejections***

The following page numbers refer to the previous Office Action (2/14/05).

The rejection of claims 3 and 31 under 35 U.S.C. § 112, first paragraph at pg 3-6 for failing to provide enablement is *withdrawn* in view of Applicants' cancellation of the claims.

The rejection of claims 1-3 and 31 under 35 U.S.C § 112, second paragraph, at pg 6 for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is *withdrawn* in view of Applicants' cancellation of claims 3 and 31 and in view of Applicant's amendments to claim 1.

***Claim Rejections - 35 USC § 112, 1st paragraph, enablement***

Claims 1, 2 and 54-57 are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claim 1 is directed to a method of testing for the remission stage of atopic dermatitis associated with a decrease in eosinophil cell number by measuring the expression level of the NOR-1 gene in eosinophils and comparing the expression level with that found in the eosinophils of a subject in the exacerbation stage of atopic dermatitis. Claim 54 is directed to a method of assessing the effect of therapy on the atopic dermatitis of a test subject by measuring NOR-1 gene expression in the eosinophil cells and comparing the expression level with that of an exacerbation stage

patient. Claim 56 is directed to a method of assessing the effect of therapy on the atopic dermatitis of an individual comprising measuring and comparing the expression level of NOR-1 gene in the eosinophil cells of the individual before and after the therapy. Claims 2, 55 and 57 limit each respective parent claim to measuring NOR-1 gene expression by cDNA PCR.

Applicants teach the gene expression level (copy/ng RNA) of the NOR-1 gene in the eosinophil cells of seven patients in the exacerbation and remission stages of atopic dermatitis (Table 5; pg 43). Individual values are reported and range from 53-3745 copy/ng RNA in the exacerbation stage, and 167-5298 copy/ng RNA in the remission stage. Applicants also detected a large decrease in the number of eosinophil cells in patients 1, 2, 3 and 5 (Table 2; pg 38).

Applicants' arguments (9/16/05; pg 14-16) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response dated 9/16/2005 Applicants submit that the claims have been narrowed from testing for any allergic disease to testing for the remission stage of atopic dermatitis that is associated with a decrease in eosinophil cell number in a test subject. Applicants submit claim 1 has been further amended to no longer recite a comparison of NOR-1 gene expression in a test subject to that in a healthy subject and such that such that the method no longer recites measuring the expression level of the NOR-1 receptor protein and instead only recites measurement of the NOR-1 gene expression level. Applicants submit that one with skill in the art would be able to test for the remission stage of atopic dermatitis associated with a decrease in eosinophil cell number in an individual by comparing the individual's NOR-1 gene expression level in eosinophil cells to that of subjects having atopic dermatitis in the exacerbation stage.

Applicants submit that the specification teaches that NOR-1 gene expression increased in association with a significant decrease in the number of eosinophil cells in individuals that have transitioned to the remission stage of atopic dermatitis. Applicants submit that the decrease in the number of eosinophil cells is a representative clinical marker for improved atopic dermatitis. Applicants' teachings are based on the results wherein four out of the seven atopic dermatitis patients in remission stage (due to

therapy) exhibited a significant decrease in number of eosinophil cells and a clear increase in the average NOR-1 gene expression. Applicants submit that the range of NOR-1 gene expression in patients showing a significant decrease in eosinophil cells with therapy is much smaller than that noted by the Examiner at pg 3-4 of the 5/13/05 Office Action; and that the increase in NOR-1 gene expression was confirmed by statistical analysis (Table 6, pg 43).

Applicants' arguments have been fully considered but are not found persuasive. The Examiner notes that the claims have been amended as indicated by Applicants. However, the amended claims lack enablement for the reasons set forth below. It is noted that Applicants' amendments, which changed the NOR-1 expression comparison between a test subject to and a healthy subject to a comparison between a test subject and an exacerbation stage subject, necessitated a change in the basis of the enablement rejection.

Applicants' remaining arguments are directed to the results in the specification that demonstrate a difference in NOR-1 gene expression between individuals in the exacerbation stage and in the remission stage who have a decrease in eosinophil cell number. The Examiner does not dispute the decrease in eosinophil number and increase in NOR-1 gene expression observed in four out of seven of the atopic dermatitis patients in the remission stage, as compared to the exacerbation stage. However, the claimed methods lack enablement for the following reasons:

1) Applicants' claims are directed to a method of diagnosing the remission stage of atopic dermatitis associated with a decrease in eosinophil cells by measuring the expression level of the NOR-1 gene. To make this diagnosis the method one of skill in the art must be able to distinguish between those subjects with atopic dermatitis who are in the exacerbation stage and those who are in the remission stage. However, the results of Table 2 and Table 5 only provide measurements for individuals with atopic dermatitis who were treated with drugs and have entered the remission stage. There is no corresponding data reported showing the level of NOR-1 gene in individuals who were treated with the same drugs but did not enter the remission stage of atopic dermatitis (i.e. remained in exacerbation stage) or healthy controls treated with the

same drugs. These individuals may or may not show similar changes in NOR-1 gene expression. The increase in NOR-1 gene expression could be due to treatment with drugs rather than due to entry into remission stage. If the drugs cause an increase in NOR-1 gene expression, using the claimed method would lead to a misdiagnosis of remission stage in any treated patient, whether or not they actually entered the remission stage. Without this information, it is not predictable whether or not NOR-1 gene expression could be used to accurately diagnose the remission stage of atopic dermatitis without further undue experimentation.

2) With respect to claims 1, 2, 54 and 55 it is noted that the claimed methods are directed to measuring NOR-1 expression in a test subject (a single individual) and comparing the results to the level in a subject in the exacerbation stage (also a single individual). Even if Applicants show that NOR-1 gene expression is not increased due to treatment alone, Applicants' results would only provide enablement for such a method if the test subject and exacerbation stage subject was the same individual. To rephrase, Applicants' method would only be enabled for a method of testing for the remission stage of atopic dermatitis comprising measuring NOR-1 gene expression in a subject in the exacerbation stage of atopic dermatitis, treating the subject, measuring NOR-1 again, and comparing the two test results, wherein the remission stage of atopic dermatitis associated with a decrease in eosinophils cell number is indicated by an increase in NOR-1 gene expression in the second measurement. However, the claimed methods lack enablement for other methods that compare single measurements between different individuals who may or may not be in the same stage of disease, and may or may not have similar levels of expression.

The term "test subject" as recited in claims 1 and 54 encompasses any subject including those that are healthy (i.e., do not have atopic dermatitis), or are in the exacerbation or remission stage of atopic dermatitis. However, the claimed methods are not enabled for taking measurements in a test subject who is healthy or in the exacerbation stage of atopic dermatitis because measuring the level of NOR-1 in the eosinophil cells of these subjects will lead to misdiagnosis. For example, assume patient 4 of Table 5 in the exacerbation stage was the test subject examined in the

claimed method. Patient 4 in the exacerbation stage has 1577 copy/ng NOR-1 RNA. A comparison to patient 7 in the exacerbation stage, who has 173.98 copy/ng NOR-1 RNA, would lead to the misdiagnosis that patient 4 was in the remission stage. The average level in all seven patients (according to Table 5) in the exacerbation stage is 934 copy/ng and the average level in the four patients (1, 2, 3, and 5) who showed increase in NOR-1 levels in remission stage is 262.24 in the exacerbation stage. Therefore, even if an average levels were used, patient 4 would be misdiagnosed.

Furthermore, even if a patient in the remission stage was used as the test subject, a comparison with a different individual in the exacerbation stage could lead to misdiagnosis according to the claimed method. If, for example, patient 4 in the remission stage was compared to any of patient 1, 2, 3, 5 or 7 in the exacerbation stage, it would lead to a misdiagnosis an increase in the level of NOR-1 would be measured. While it is true that patient 6 is in the remission stage, the claimed method requires diagnosis of the remission stage associated with a decrease in eosinophil cell. Patient 4 in the remission stage actually increased numbers of eosinophil cells according to Table 2, and a decrease in NOR-1 expression. Only by measuring the same individual in the exacerbation stage and the remission stage could an increase in the NOR-1 gene expression be confirmed.

3) With respect to claims 56 and 57, the claims are drawn to "assessing the effect of a therapy on the atopic dermatitis of an individual" wherein an "increase in NOR-1 gene expression level after the therapy compared to that before the therapy indicates an improvement in the symptoms of the atopic dermatitis" and a "positive effect of said therapy on the atopic dermatitis". These claims are enabled for an "increase in the NOR-1 gene expression" indicating "an improvement in the symptoms of the atopic dermatitis and a positive effect of said therapy" only in so far as the increase indicates that the individual in the exacerbation stage has entered the remission stage associated with a decrease in the number of eosinophil cells. The claims however, broadly encompass other improvements in the symptoms or positive effects that are not linked to the remission stage associated with a decrease in the number of eosinophil cells. Furthermore, these claims lack enablement for an individual

with atopic dermatitis who is already in the remission stage; Applicants have not shown that further treatment will cause an "improvement in the symptoms" or "positive effect", even in NOR-1 levels increase.

For the reasons set forth, without further guidance a person of ordinary skill in the art would not be able to make and/or use the invention as claimed without undue experimentation. Due to the large quantity of experimentation necessary to determine if the method could be used to diagnostically to test for the remission stage of atopic dermatitis associated with a decrease in the number of eosinophil cells, the lack of direction/guidance presented in the specification regarding same, lack of working examples and the teachings of the prior art and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use the claimed invention. What Applicant has provided is a mere wish or plan and an invitation to experiment to determine whether the method could be used to test for the remission stage of atopic dermatitis associated with a decrease in the number of eosinophil cells.

***Conclusion***

No claims are allowed.

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 571-272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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